Infant neuromotor development: an early indicator of genetic liability for neurodevelopmental disorders

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Childhood neurodevelopmental disorders include autistic spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), communication disorders, learning disabilities and developmental motor-co-ordination problems among others (1). These conditions typically are considered to originate early in development, although there have been recent, controversial challenges to this assumption for ADHD (2). Childhood neurodevelopmental disorders, regardless of whether they are defined as diagnostic categories or traits, show strong phenotypic and genetic overlaps with each other(1). It is also well known that autism can be preceded by very early motor and sensory developmental problems (3) such as motor "floppiness", delayed motor milestones and hypersensitivity to sensory stimuli. These are non-specific markers of atypical development because they may also index global developmental delay and predate other disorders including schizophrenia(4) and ADHD (3). However, these early indicators of atypical development are sometimes overlooked in the psychiatric literature.

In this issue of Biological Psychiatry, Serdarevic and colleagues(5) address this important gap in Generation R, a prospective, population-based cohort from Rotterdam in the Netherlands; they use data from almost 2000 individuals of European ancestry. The authors directly examine neuromotor development in infants aged 9 to 20 months and subsequently assess autistic traits in these children at age 6, using a parent-reported questionnaire. The authors are to be commended because the neuromotor assessment was conducted directly with the infant at home using a modified version of the Touwen's Neurodevelopmental Examination. This provides a very different measure to the ones typically used in Psychiatry that rely on reported symptoms. The authors then derived a construct called "neuromotor development" that consisted of different sub-scales including high and low muscle tone, infant responses and a wide variety of other observations such as startle and eye fixation. Their aim was to test whether ASD and ADHD genetic liability is associated with suboptimal infant motor and sensory development. This was achieved using two methods: first, by testing association between ADHD and ASD polygenic risk scores (PRS) and neuromotor development and

second, by assessing SNP co-heritability between ASD and motor development (using GREML: the genomic-relatedness-based restricted maximum-likelihood approach)(6).

Polygenic risk scores (PRS) are a composite measure of "risk" alleles (7) identified from an independent, discovery genome-wide association (GWAS) data set. They have been found to provide useful indicators of disease risk but are only weakly predictive.

As might be expected, given that ADHD and ASD diagnoses show genetic correlation (8), both ASD and ADHD PRS were observed to be associated with ASD traits at age 6 years (boys only for ADHD PRS). The novel finding is that ASD PRS was also associated with directly assessed overall infant neuromotor functioning. In terms of specific sub-scale outcomes: ASD PRS were associated with low muscle tone and high ADHD PRS were associated with lower scores on the measure of "senses and other observations". Associations were most consistent in boys. Using the SNP-based heritability approach, both autistic traits and motor development were observed to be heritable and the authors observed a moderate genetic correlation of 0.32 (SE=0.17) between overall motor tone and autistic traits.

The strengths of this paper are that it utilizes a prospective, population-based cohort design and therefore avoids clinical referral selection and infant development is assessed directly. The authors also focus on an important developmental period. The limitations, many of which are highlighted by the authors, include the current weak predictive power of ASD and ADHD PRS and the inconsistency of findings across different p-value thresholds for ADHD and ASD PRS. Also, it is worth highlighting that SNP heritability, unlike twin heritability captures only a small component of genetic variation. Another problem that the authors encountered is a global concern (9). At present, GWAS data lack diversity and overwhelmingly represent individuals of European descent. This means that the authors were forced to restrict their analyses to those of European ancestry even though the full Generation R cohort is ethnically diverse. Another issue to consider is that ASD is examined as a trait

not as a diagnosis measure in this population-based cohort. However there is growing evidence from the perspective of genetics at least that there is genetic overlap between ASD traits and disorder (10). As data on ASD or ADHD traits prior to the age of 6 years are not presented, it is intriguing as to whether the early developmental problems genuinely precede the emergence of core ASD features.

What do the findings mean? First, they suggest that the same genetic liability which contributes to ASD also indexes sub-optimal infant motor development. Genetic correlations between different neurodevelopmental and neuropsychiatric disorders are now well established. The findings of this study highlight additional genetic overlap between childhood neurodevelopmental disorders and early neuromotor and sensory development. These findings concur with those emerging from high-risk studies of infants at elevated familial risk for autism(3). Those investigations also suggest that familial/genetic liability is indexed by very early developmental signs in infancy. What is important to know is whether these are causal antecedents, disorder precursors or simply developmental accompaniments to ASD.

Most individuals with sub-optimal motor and sensory development in the general population will not necessarily go onto develop a full-blown clinical diagnosis of autism. Thus, some important clinical questions remain. What influences the transition from impaired neuromotor development to the complete manifestation of autism? Can the underlying biological processes and developmental trajectory be altered or are the early developmental manifestations simply an initial signpost of underlying genetic liability and the developmental processes underlying the emergence of autism will unfold regardless? The findings of this study further raise the practical issue of whether regular screening for ASD (and other neurodevelopmental disorders) is warranted in all infants who show sub-optimal development. This clearly would require evaluation. As is often the case with any

interesting study, the findings highlight the need for replication and extension, additional hypotheses to test, and a series of important questions to resolve in the future.

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References

1. Thapar A, Cooper M, Rutter M (2017): Neurodevelopmental disorders. *The lancet Psychiatry*. 4: 339–346.

2. Asherson P, Agnew-Blais J (2019): Annual Research Review: Does late-onset attention-deficit/hyperactivity disorder exist? *J Child Psychol Psychiatry*. 60: 333–352.

3. Johnson MH, Gliga T, Jones E, Charman T (2015): Annual Research Review: Infant development, autism, and ADHD - early pathways to emerging disorders. *J Child Psychol Psychiatry*. 56: 228–247.

4. Filatova S, Koivumaa-Honkanen H, Hirvonen N, Freeman A, Ivandic I, Hurtig T, *et al.* (2017): Early motor developmental milestones and schizophrenia: A systematic review and meta-analysis. *Schizophr Res*. 188: 13–20.

5. Serdarevic F, Tiemeier H, Jansen P, Alemany S, Xerxa Y, Neumann A, *et al.* (n.d.): Polygenic risk scores for developmental disorders, neuromotor functioning during infancy and autistic traits in childhood. *Biol Psychiatry*.

6. Yang J, Lee SH, Goddard ME, Visscher PM (2011): GCTA: A Tool for Genome-wide Complex Trait Analysis. *Am J Hum Genet*. 88: 76–82.

7. Martin AR, Daly MJ, Robinson EB, Hyman SE, Neale BM (2019): Predicting Polygenic Risk of Psychiatric Disorders. *Biol Psychiatry*. 86: 97–109.

8. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, *et al.* (2019): Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet*. 51: 63–75.

9. Sirugo G, Williams SM, Tishkoff SA (2019): The Missing Diversity in Human Genetic Studies. *Cell*.

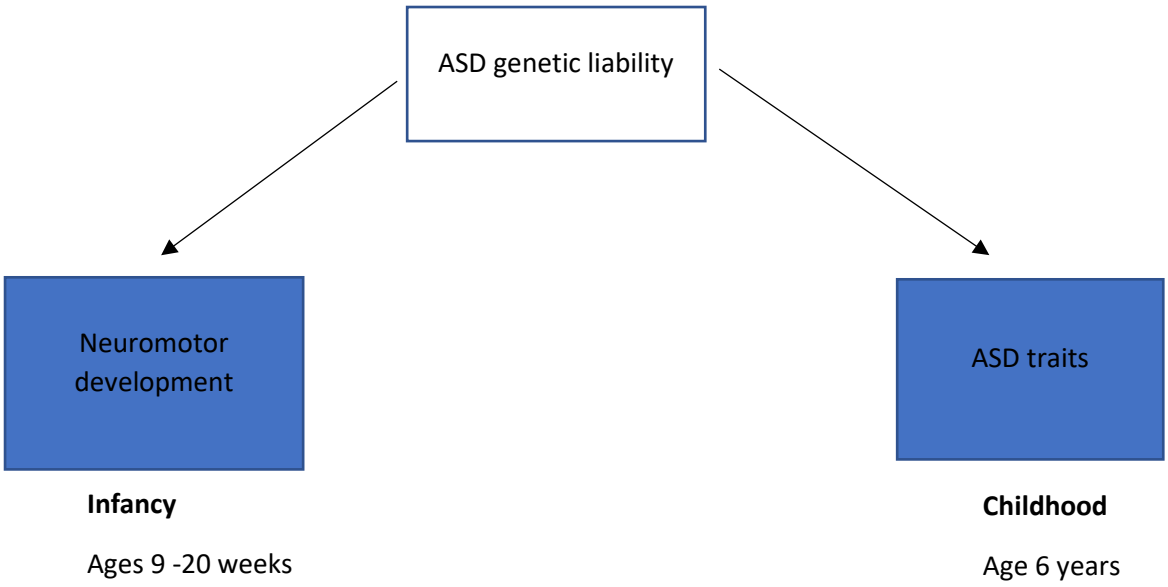
177: 26–31.

10. Robinson EB, St Pourcain B, Anttila V, Kosmicki JA, Bulik-Sullivan B, Grove J, *et al.* (2016): Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population. *Nat Genet*. 48. doi: 10.1038/ng.3529.

Figure 1

ASD genetic liability association with infant neuromotor development and ASD traits at age 6 years

Figure 1


ASD genetic liability
Neuromotor development
ASD traits
Infancy
Ages 9 -20 weeks
Childhood
Age 6 years